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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/830,839	02/19/2002	Ajit Lalvani	7096-102XX / 10103632	3551

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EXAMINER	
MINNIFIELD, NITA M	

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 06/29/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/830,839	LALVANI ET AL.	
	Examiner	Art Unit	
	N. M. Minnifield	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 April 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *75,76,78,79 and 83-87* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *75,76,78,79 and 83-87* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on April 7, 2006 has been entered.

2. Claims 75, 76, 78, 79 and 83-87 are now pending in the present application. All rejections have been withdrawn in view of Applicants' amendment to the claims and/or comments, with the exception of those discussed below.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. Claims 75, 76, 78, 79 and 83-87 are rejected under 35 U.S.C. 103(a) as being unpatentable over Andersen et al (5955077).

The claims are directed to methods of determining infection in an human patient by, or exposure of a human patient to mycobacterium which expresses ESAT-6 comprising the method of contacting a population of T cells from the patient with a panel of peptides consisting of peptides of SEQ ID NO: 1 to 8 and optionally other peptides from SEQ ID NO: 9-11, and to kits for carrying out the method. The peptides can also be a peptide wherein the peptide is substituted by an analogue; the peptide analogue has one or more end-terminal deletions.

Andersen et al teaches the polypeptide ESAT-6 as well as the amino acid sequence (SEQ ID NO: 2). The peptides (SEQ ID NO: 1-11) claimed by Applicants are set forth in disclosed SEQ ID NO: 2. The prior art teaches methods for diagnosing tuberculosis (abstract; col. 11). Andersen et al teaches that analogues and subsequences of the polypeptides can be used so long as it has the same immunological characteristics as the polypeptide (col. 2, l. 50-55). The analogue and subsequence of the polypeptide are of a "...similar amino acid sequence as shown in SEQ ID NO: 2, allowing for minor variations which do not have adverse effect on the ligand binding properties and/or biological function and/or immunogenicity, or which may give interesting and useful novel binding properties or biological functions and immunogenicities etc." (col. 2, l. 60-67). "Furthermore, in the present context the term "immunologically equivalent" means that the analogue or subsequence of the polypeptide is functionally equivalent to the polypeptide with respect to the ability of evoking a protective immune response against tuberculosis and/or eliciting a diagnostically significant immune response (e.g. a DTH reaction)." (col. 3, l. 4-10; see also col. 3, l. 41-47). Andersen et al teaches various types of immunoassays such as ELISAs, immunoblot techniques, RIAS, other non-enzyme linked antibody binding assays, etc. (col. 12, l. 15-29). Andersen et al teaches that in immunodiagnostics it is often possible and practical to prepare antigens from segments of a known immunogenic protein or polypeptide, that certain epitopic regions may be used to produce responses similar to those produced by the entire antigenic polypeptide, and that these potential antigenic or immunogenic regions can be identified by known methods (col. 11, l. 9-25). Andersen et al teaches a peptide, which comprises an epitope for a T-helper cell (col. 11, l. 27-28 comprising intradermally injecting, in the animal, a

pharmaceutical composition containing a polypeptide as defined or an analogue and/or subsequence thereof which is immunologically equivalent to the peptide, a positive skin response at the location of injection being indicative of the animal having tuberculosis, and a negative skin response at the location of injection being indicative of the animal not having tuberculosis (col. 14, l. 6-17). Andersen et al teaches that when "diagnosis of previous or ongoing infection with virulent mycobacteria is the aim, a blood sample comprising mononuclear cells (i.e. T-lymphocytes) from a patient could be contacted with a sample of one or more polypeptides of the invention. This contacting can be performed in vitro and a positive reaction could e.g. be proliferation of the T-cells or release cytokines such as γ-interferon into the extracellular phase (e.g. into a culture supernatant). Finally, it is also conceivable to contact a serum sample from a subject to a contact with a polypeptide of the invention, the demonstration of a binding between antibodies in the serum sample and the polypeptide being indicative of previous or ongoing infection." (col. 14, l. 35-47; see also col. 14, l. 48-62; figures; Example 5, cols. 29-30). Andersen et al teaches the use of ESAT6 as a diagnostic agent on a skin test (see Example 6, col. 31, l. 5-17). Andersen et al teaches that the mycobacterium can be *M. tuberculosis*, *M. bovis* or *M. africanum* (col. 2, l. 27-31). Andersen et al teaches diagnostic kits for the diagnosis of on-going or previous TB infections comprising peptides and means for detecting the interaction with the relevant substance reacting with peptide (col. 12, l. 30-43).

The prior art of Andersen et al does not specifically teach the individually claimed peptides as set forth in SEQ ID NO: 1-11. However, Andersen et al teaches that ESAT-6 is a protein that has been identified as one useful in the diagnosis of tuberculosis and that subsequences of the protein can be used so long

as it has the same immunological characteristics and that subsequences of the ESAT-6 can be used in diagnostic methods. Andersen et al teaches that in immunodiagnostics it is often possible and practical to prepare antigens from segments of a known immunogenic protein or polypeptide that certain epitopic regions may be used to produce responses similar to those produced by the entire antigenic polypeptide as well as methods of preparing these antigenic segments (i.e. peptides). It would have been to a person of ordinary skill in the art at the time the invention was made to use the teachings of Andersen et al to develop methods of diagnosing tuberculosis or mycobacterium infection in a patient using the ESAT-6 protein since the art teaches its use, as well as determining segments of the ESAT-6 that function in the same manner as the complete ESAT-6 protein and use them for diagnostic purposes. The amino acid sequence of the ESAT-6 is known in the art (Andersen et al teaches the sequence). It is also known in the art as set forth in Andersen et al to identify segments, subsequences or epitopes of a polypeptide that can be used in diagnostic methods for the purpose of developing a more sensitive diagnostic methods for detection of tuberculosis or mycobacterium infection in a patient. It is also noted that the claims do not set forth that the claimed method is an improvement over the known methods of tuberculosis diagnosis Applicants have asserted that the claimed invention is a highly advantageous and clinically useful diagnostic test for M. tuberculosis infections in humans. However, the specific advantageous and improvements over those methods of Andersen et al have not been set forth in the claims, nor has there been a comparison (side-by-side or otherwise) with regard to the prior art to show that the claimed methods are more sensitive, yield fewer false positive, or any other property to distinguish the claimed method over the prior art. The claimed

invention is prima facie obvious in view of the teachings of Andersen et al absent any convincing evidence to the contrary.

It is noted that a US Patent is presumed valid and enabled. Since every patent is presumed valid (35 U.S.C. 282), and since that presumption includes the presumption of operability (Metropolitan Eng. Co. v. Coe, 78 F.2d 199, 25 USPQ 216 (D.C. Cir. 1935), examiners should not express any opinion on the operability of a patent. Affidavits or declarations attacking the operability of a patent cited as a reference must rebut the presumption of operability by a preponderance of the evidence. In re Sasse, 629 F.2d 675, 207 USPQ 107 (CCPA 1980).

Further, since in a patent it is presumed that a process if used by one skilled in the art will produce the product or result described therein, such presumption is not overcome by a mere showing that it is possible to operate within the disclosure without obtaining the alleged product. In re Weber, 405 F.2d 1403, 160 USPQ 549 (CCPA 1969). It is to be presumed also that skilled workers would as a matter of course, if they do not immediately obtain desired results, make certain experiments and adaptations, within the skill of the competent worker. The failures of experimenters who have no interest in succeeding should not be accorded great weight. In re Michalek, 162 F.2d 229, 74 USPQ 107 (CCPA 1947); In re Reid, 179 F.2d 998, 84 USPQ 478 (CCPA 1950).

The rejection is maintained for the reasons of record. Applicant's arguments filed ***August 4, 2005*** have been fully considered but they are not persuasive. Applicants have asserted that Andersen et al merely confirmed that whole ESAT-G will produce a T cell response when utilized in a skin test in guinea pigs, and cannot be validly combined with any other reference to suggest obvious-ness of a peptide panel as specified by the claims in this application. However, this obviousness rejection is based on the teachings of Andersen et al (5955077) only. Applicants have asserted that Andersen et al does not provide a basis for assuming

that all predominant HLA specificities could be represented by at least one member of a small panel of short peptides. However, these characteristics or properties are not set forth in the claims. Andersen et al teaches that diagnosis of infection comprises obtaining a blood sample comprising mononuclear cells (T lymphocytes) from a patient and then to contact the sample with the peptide. The contacting can be performed in vitro and a positive reaction could be proliferation of the T-cells or release of cytokines such interferon-gamma (see col. 14). Applicants have asserted that a major technical improvement has been achieved by using the ESAT-6 peptide panel and referred to Example 6 of the specification. However, the claims do not recite that this method is an improvement over the known diagnostics now used. Applicants have asserted that Chapman et al 2002 substantiates Applicants' work and that this method is an improvement. However, this reference was published after Applicants' effective filing date. It is not clear that the methods and data set forth in Chapman et al were obtained by the claimed methods and the methods set forth in the pending specification. Does Applicants' specification teach that the claimed method is more sensitive and specific than the currently used diagnostic methods? Andersen et al suggests the claimed method. Applicants have used Elhay et al (Infection and Immunity, 1998, 66/7:3454-3456) to indicate that Andersen et al were not advocating use of any panel of ESAT-6 fragments for diagnostic use in humans, but rather suggesting that at that time that a good diagnostic reagent for use with humans would be a combination of whole ESAT-6 with another protein (see Elhay et al, 1998). However, the issued patent of Andersen et al teaches one of ordinary skill in the art at the time the invention was made the analogues and subsequences of the ESAT-6 polypeptide can be used for diagnosis of mycobacterium infection in a human patient, using the same methods steps as set forth in Applicants' instant claims. Applicants have asserted that it is not disputed that Andersen et al teaches diagnostic utility of ESAT-6 and speculated subsequences of ESAT-6 might be similarly employed. However, Applicants have asserted that the improvements are taught in Andersen et al. That being: the immunological and clinical advantages achieved through the use of an ESAT-6 peptide panel as clamed, namely improved 'access' in the assay to the entire spectrum of CD4+/CD8+ T cells, and compatibility with a broad spectrum of human HLA specificities, could not have been predicted from the Andersen et al teachings relied on by the Examiner. However, it is the Examiner's position that none of these improvements, immunological and clinical advantages, improved 'access', etc are set forth in the instant claims. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

As previously stated the teachings of Andersen et al as a whole would have been obvious to a person of ordinary skill in the art at the time the invention was made, absent any convincing evidence to the contrary.

The rejection is maintained for the reasons of record as previously set forth. Applicant's arguments filed April 7, 2006 have been fully considered but they are not persuasive. It is noted that Applicants' arguments have been previously addressed. With regard to the favorable examination report in relation to the corresponding European patent application it is noted that examination considerations for a US patent application are quite different from examination considerations for EPO and other Authorities. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., improvements in both specificity and sensitivity) are not recited in the rejected claims. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Applicants have asserted that claim 1 of Andersen proposes to test for subsequences relying on T cells from mice-infected with tuberculosis and that such a test using animal T cells is not suitable for identifying any human epitopes. However, it is noted that the entirety of the Andersen patent is considered for its teachings not the issued claims. Andersen et al teaches methods of diagnosing tuberculosis caused by *M. tuberculosis*, *M. bovis* or *M. africanum* in an animal, including a human being, as well as diagnosis of previous or ongoing infection with virulent mycobacteria is the aim, a blood sample comprising mononuclear cells (i.e. T-lymphocytes) from a patient could be contacted with a sample of one or more polypeptides of the invention. This contacting can be performed in vitro

and a positive reaction could e.g. be proliferation of the T-cells or release cytokines such as γ-interferon into the extracellular phase (e.g. into a culture supernatant). Absent any convincing evidence or unexpected results to the contrary, the claimed invention is prima facie obvious in view of teachings of Andersen et al.

5. No claims are allowed.

6. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to N. M. Minnifield whose telephone number is 571-272-0860. The examiner can normally be reached on M-F (8:00-5:30) Second Friday Off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette R.F. Smith can be reached on 571-272-0864. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

N. M. Minnifield
Primary Examiner
Art Unit 1645

June 22, 2006